11:30

801-5 Prooxidative Effects of Nitroglycerin in Hyperlipidemic Animals: Oxidative Stress in Vasculature as an Initiating Event Leading to Impaired Endothelial Relaxation and Increased Plasma Oxidation

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Background: Early stages of atherosclerosis have been shown to be associated with endothelial dysfunction secondary to decreased endothelial nitric oxide (•NO) bioactivity following reaction with endothelial superoxide ($•O_2^-$). In vitro experiments demonstrated potent antiatherosclerotic effects of •NO suggesting that treatment with •NO (e.g. via organic nitrates) could compensate for the diminished availability of endothelial •NO. Nitric oxide, however, may also react with endothelial-derived $•O_2^-$ in order to form the potent oxidant and inhibitor of vascular function peroxynitrite ($ONOO^-$).

Methods and Results: We treated Watanabe rabbits (heritable model of hyperlipidemia) for a 3 d period with nitroglycerin (NTG) patches. Endothelial function was determined using the endothelium dependent vasodilator acetylcholine (ACh) in isometric tension studies. Relative rates of vascular $•O_2^-$ production were determined using the lucigenin assay. We also tested the influence of in vivo NTG treatment on oxidative stress, as indicated by lipophilic and hydrophilic antioxidant depletion in plasma and plasma oxidizability. In intact vessels of hyperlipidemic animals, $•O_2^-$ production 2 fold increased as compared to controls and NADH-oxidase activity was significantly greater than controls. NTG treatment of hyperlipidemic animals decreased the lucigenin signal but increased NADH-oxidase activity suggesting increased vascular peroxynitrite formation. NTG treatment also decreased plasma levels of α and β-carotene while having no significant effects on hydrophilic antioxidant levels. In vitro, NTG-exposure reduced plasma oxidizability while increasing it following in vivo treatment.

Conclusions: These observations suggest that short-term treatment of hyperlipidemic animals with NTG worsens rather than improves endothelial dysfunction. The increase in plasma oxidizability and decrease in lipophilic antioxidant levels reflects increased oxidative stress within the vasculature.

11:45

801-6 Lack of Efficacy of Intravenous Basic Fibroblast Growth Factor in Promoting Myocardial Angiogenesis

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Background: Basic fibroblast growth factor (bFGF) is in clinical trials as an angiogenic agent in ischemic cardiovascular disease; however, its optimal route of administration is unknown. We have shown that bFGF promotes coronary collateral expansion when administered by a systemic arterial route (left atrium) or by direct intracoronary injection. The intravenous (IV) route has obvious practical advantages over arterial routes; however, it has not been carefully evaluated in the context of myocardial angiogenesis. Using a bFGF dose and schedule that were previously found to be effective following systemic arterial administration, we tested repetitive IV bFGF infusion as a means to promote myocardial collateral development in our established dog model.

Methods: Mongrel dogs underwent placement of ameroid constrictors on the left circumflex coronary artery. Animals were randomized to receive bFGF 100 μg/kg daily (n = 7) or placebo (n = 9) as a 3–4 hour IV infusion, days 10 through 16 after instrumentation.

Results: Collateral perfusion, assessed with fluorescent microspheres during maximal chromonar-induced vasodilation, was equivalent in both groups at all time points (10, 17, 24, 31 and 38 days after ameroid placement).

Conclusions: IV bFGF was ineffective in myocardial angiogenesis likely because of first pass lung uptake by low affinity receptors. These findings raise concerns regarding use of IV bFGF administration for myocardial angiogenesis in future clinical trials.

802 Clinical Trials With Antiplatelet Agents During Interventional Procedures

Monday, March 30, 1998, 10:30 a.m.–Noon
Georgia World Congress Center, Lecture Hall 2

10:30

802-1 Abciximab Reduces Urgent Target Vessel Revascularization at 30 Days After Primary Angioplasty, Independently of Acute Angiographic Results. The RAPPORT Trial

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Background: Recurrent ischemia leading to urgent revascularization immediately after primary angioplasty is caused by abrupt vessel closure, related to residual thrombosis, obstructing dissections, or less than optimal coronary flow. Abciximab reduces ischemic complications of PTCA, but was not tested in primary angioplasty.

Methods: Pts with acute MI < 12 hr. were randomized to placebo (P, n = 242) or abciximab (A, n = 241) as an adjunct to primary angioplasty. Death, reinfarction and recurrent ischemia leading to urgent target vessel revascularization (TVR) at 7 and 30 days, and angiograms were independently analyzed centrally.

Results: Outcomes at 30 days among pts receiving study drug (89% of those enrolled):

	P (n = 213)	A (= 216)	p value
Post PTCA stenosis	37% [16,48]	38% [28,46]	0.59
Post PTCA TIMI III	85%	87%	0.53
Composite	10.3%	4.9%	0.03
Death	1.9%	1.8%	0.83
Reinfarction	4.7%	2.7%	0.25
TVR	5.6%	1.8%	0.03

Conclusion: As compared with placebo, abciximab markedly reduces need for urgent TVR at 30 days. This occurred despite similar acute angiographic results and highlights the contribution of vessel wall passivation provided by abciximab to the prevention of recurrent ischemic events.

10:45

802-2 Complementarity of Stenting and Abciximab for Percutaneous Coronary Intervention

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The role of abciximab (A) platelet GP IIb/IIIa blockade in patients (pts) with coronary stent placement has not been determined. Stents (S) were placed in 529 patients in the combined EPIC (n = 7), EPILOG (n = 382) and CAPTURE (n = 140) placebo (P) controlled randomized trials of A therapy. S were provisional or planned (EPILOG stent substudy) in 473 and 56 pts respectively. Clinical events for Pts randomized to A (n = 308) or P (n = 221), hazard ratio (HR) and 95% confidence intervals (CI) are shown. Survival was enhanced and the occurrences of death/MI, death/MI/Urg Int or TVR were reduced in A treated pts.

Event %	30 Day				6 Month			
	P	A	HR	CI	P	A	HR	CI
Death	1.4	0	*		2.3	1.0	0.39	(0.09, 1.64)
Death/MI	18.6	6.5	0.32	(0.19, 0.56)	20.4	8.5	0.38	(0.24, 0.62)
Death/MI/Urg Int	20.8	8.1	0.36	(0.22, 0.58)	22.6	11.1	0.46	(0.28, 0.77)
Death/MI/TVR	20.8	10.1	0.44	(0.28, 0.70)	30.0	22.4	0.67	(0.48, 0.95)
Urg Int	7.7	2.0	0.23	(0.09, 0.59)	8.9	2.5	0.27	(0.10, 0.71)
TVR	8.6	3.9	0.41	(0.20, 0.85)	19.4	14.6	0.70	(0.46, 1.07)

(*P = 0.04; TVR = target vessel revascularization; URG INT = Urgent Intervention)

These randomized trials demonstrate prophylactic A improves outcomes in pts following provisional-unplanned coronary stent placement. Extrapolation of these findings to elective stenting requires study in an ongoing dedicated trial.

MONDAY ORAL